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Original Research Article

An Estimate of Attributable Cases of Alzheimer Disease and Vascular Dementia due to Modifiable Risk Factors: The Impact of Primary Prevention in Europe and in Italy

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Keywords
Alzheimer disease · Vascular dementia · Prevention · Public health · Attributable cases

Abstract
Background: Up to 53.7% of all cases of dementia are assumed to be due to Alzheimer disease (AD), while 15.8% are considered to be due to vascular dementia (VaD). In Europe, about 3 million cases of AD could be due to 7 potentially modifiable risk factors: diabetes, midlife hypertension and/or obesity, physical inactivity, depression, smoking, and low educational level. ***Aims:*** To estimate the number of VaD cases in Europe and the number of AD and VaD cases in Italy attributable to these 7 potentially modifiable risk factors. ***Methods:*** Assuming the nonindependence of the 7 risk factors, the adjusted combined population attributable risk (PAR) was estimated for AD and VaD. ***Results:*** In Europe, adjusted combined PAR was 31.4% for AD and 37.8% for VaD. The total number of attributable cases was 3,033,000 for AD and 873,000 for VaD. In Italy, assuming a 20% reduction of the prevalence of each risk factor, adjusted combined PAR decreased from 45.2 to 38.9% for AD and from 53.1 to 46.6% for VaD, implying a 6.4 and 6.5% reduction in the prevalence of AD and VaD, respectively. ***Conclusion:*** A relevant reduction of AD and VaD cases in Europe and Italy could be obtained through primary prevention.

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Introduction

Dementia is currently considered as one of the greatest global challenges for health and social care in the 21st century. The constantly growing number of cases, along with the lack of disease-modifying treatment and the socioeconomic impact of its management, are a serious threat to the sustainability of our health care system.

The number of cases of dementia in Europe is estimated to increase from 7.7 million in 2001 to 15.9 million in 2040 [1]. Up to 53.7% of all cases of dementia are assumed to be due to Alzheimer disease (AD), while 15.8% are considered to be due to vascular dementia (VaD) [2].

Thus, the interest in identifying and implementing effective preventive strategies is considerably growing. Delaying the onset of dementia and reducing the occurrence of “avoidable” cases may have, in fact, enormous public health implications.

Norton et al. [3] reported that, in Europe, about 3 million cases of AD could be due to potentially modifiable risk factors such as diabetes, midlife hypertension and/or obesity, physical inactivity, depression, smoking, and low educational level.

This study provided preliminary information on the possible magnitude of primary prevention strategies for dementias [3]. However, despite these major breakthroughs in the field, some issues that should deserve more attention still remain poorly addressed.

Specific issues on the transferability of available data on preventable cases to specific regions and countries have not yet been discussed in enough detail. The estimates obtained at a global level may only be partially adequate as a basis for policies targeted to specific geographic and cultural settings, due to differences in the prevalence of risk factors and their possible interactions. The few reports available on this topic showed a relevant variability of estimates across different areas worldwide. However, data from local longitudinal surveys and national surveillance systems may allow to better estimate the proportion of locally preventable cases. This shift from a global perspective to a local perspective might support public health considerations and strategies in a more precise and accurate way.

Italy is currently the second country, after Germany, with the highest proportion of elderly people (≥65 years) in Europe, with an estimated 1 million subjects having dementia [4]. However, the issue of primary prevention is still neither included in a national dementia plan, through some specific recommendations [5], nor listed in the action plan for the prevention and control of noncommunicable diseases in the WHO European region [6].

The Italian national dementia plan, on the other hand, includes “promoting strategies of primary and secondary prevention” as the first priority among the 4 actions of objective 1 (“promote health and social care interventions and policies”) [4]. Moreover, the Italian national prevention plan also provides a qualitative and quantitative tool to assess the impact of its components both at a national and at a local level [7]. In this context, a quantitative estimate of the possible efficacy of promoting prevention strategies is thus urgently needed.

The aims of the present study were: (a) to estimate the number of VaD cases attributable to potentially modifiable risk factors in Europe, thus filling a gap in the literature concerning the potential for primary prevention of the second most common type of dementia; and (b) to estimate, in Italy, at the national and regional level, the number of AD and VaD cases that may be halted by acting on modifiable risk profiles. The focus on the individual Italian regions captures the local variability of the phenomenon and reflects the need for locally oriented public health responses.

Materials and Methods

Data Sources

Several different data sources were used to estimate each component of the combined population attributable risk (PAR) for AD and VaD in both Europe and Italy.

The estimated PAR includes three components: the prevalence of each risk factor in the area of interest, communality of each risk factor, and the risk ratios (RRs) for each risk factor for either AD or VaD.

Europe

The components of the combined PAR for AD and the number of attributable cases in 2010 were already available in the study by Norton et al. [3]. Specifically, the authors stated that the prevalence of each risk factor was obtained from previous studies, the RR for each risk factor was found searching the most updated studies published between January 2005 and May 2014, and the proportion of the variance in each risk factor shared with the other 6 factors (communality) was estimated based on data from the 2006 Health Survey for England [8]. The estimated number of preventable cases was then estimated using the number of prevalent cases of AD in Europe reported in a previous study by Brookmeyer et al. [9].

For the analyses on VaD, the prevalence and the communality of each risk factor reported in the study by Norton et al. [3] were used. Moreover, data on the RRs were obtained with the same bibliographic search strategy as applied by the authors, but limiting the search to VaD and considering studies published from January 2005 to June 2017. The following search terms were, thus, used: ((“diabetes mellitus” OR “hypertension” OR “obesity” OR “smoking” OR “depression” OR (“cognitive activity” OR “education”) OR (“physical inactivity” OR “exercise”)) AND (Alzheimer OR “dementia”)) AND (“Vascular dementia” OR “VaD”).

Italy

The same RRs for the 7 risk factors considered in the analyses for Europe were used for both AD and VaD. The prevalence of the 7 risk factors in each Italian region was obtained using the official data from the PASSI (Progressi delle Aziende Sanitarie per la Salute in Italia – Progresses by local health units towards a healthier Italy) surveillance system for the years 2013–2016 [10–12]. The shared variance for each risk factor was calculated using the PASSI database by carrying out a principal-component analysis on the tetrachoric correlation matrix, adopting the Kaiser criterion to choose the number of factor to be considered.

The PASSI surveillance system is an ongoing behavioral risk factor surveillance system. It collects information on health-related behaviors associated with chronic, noncommunicable diseases in adult subjects (18–69 years) residing in Italy. The system was first implemented in 2007 and has been active since 2008. It was designed as a tool to support prevention plans in achieving the health-related goals set by the National Health Plan.

The units of analysis in the PASSI system are the local health units (LHU). The surveyed population includes adults (18–69 years) residing in each LHU area having an active telephone number. From this population, a representative sample of adults is randomly selected for interviews each month. The sample is also stratified according to age groups (18–34, 35–49, and 50–69 years) and gender, proportionally to the size of the same strata in the general population.

Telephone interviews are carried out by specifically trained LHU personnel using a standardized questionnaire. The questionnaire is designed to gather information on several topics, including smoking habit, physical activity/inactivity, weight, alcohol consumption, fruit and vegetable consumption, cardiovascular risks, compliance to cancer screenings, compliance to safety measures for the prevention of car and/or workplace accidents, vaccination against flu, physical and psychological well-being, and other aspects of health-related quality of life.

A total of 146,526 subjects from 124 out of 139 Italian LHU (89%) were interviewed in the years 2013–2016. Participants were representative of 90% of the Italian population. The 7 considered risk factors were defined as follows:

Hypertension: responders were defined as having hypertension if they reported a diagnosis of hypertension provided by a physician.

Obesity: responders were defined as being obese if they had a body mass index (BMI) ≥30. BMI was calculated as self-reported weight divided by the square of self-reported height in meters (kg/m^2).

Diabetes: responders were defined as having diabetes if they reported a diagnosis of diabetes provided by a physician.

Physical activity/inactivity: physical activity was measured asking responders if they had engaged in either moderate (cleaning, gardening, walking at a fast pace, riding a bicycle) or vigorous (running, aerobic exercise, any type of heavy work) physical leisure activities during the 30 days before the interview. For both levels of activity, participants were asked to report the average number of days per week and hours per day they were engaged in the reported activities. The product of the two values was obtained for both levels of activity, and an overall measure of physical activity per week was obtained for each level. Assuming that 1 min of vigorous physical activity was equivalent to 2 min of moderate physical activity, the overall measure was calculated by doubling the number of minutes of vigorous physical activity, and adding the total to the number of minutes of moderate activity. Reported activities with lengths <10 min were not included. According to the WHO, responders were considered as physically inactive if they reported a number of minutes of physical activity <10 [13].

Symptoms of depression: the PASSI system investigates symptoms of dementia using the Patient Health Questionnaire 2 [14], a screening tool including two questions asking respectively the number of days in the past 2 weeks during which the subject experienced a lack of interest or pleasure in doing usual activities, and the number of days, in the same time span, during which the subject felt down, depressed, or hopeless. Answers to both questions can range from 0 to 14 days. The number of days is then scored using a 4-point scale ranging from 0 to 3 with 0–1 days scored as 0, 2–6 days scored as 1, 7–11 days scored as 2, and 12–14 days scored as 3. The total score is then calculated as the sum of single scores and subjects with a score ≥3 are considered as having depressive symptoms.

Smoking: subjects are classified as current smokers if they report having smoked at least 100 cigarettes during their lifetime and are currently still smoking either every day or even occasionally.

Low educational level: subjects are classified as having a low educational level if they did not attend any type of school or if they completed only elementary school or junior high school.

Informed consent in this study is not necessary because the paper is based on the published epidemiological data and on data from active surveillance systems in the general population. Our study has been performed according to the Italian National Plan on Dementia.

Analyses

Prevalent Cases of AD and VaD

The number of prevalent cases of VaD in Europe was obtained by applying the 15.8% proportion estimated by Lobo et al. [2] to the total number of prevalent cases of dementia in Europe estimated by Brookmeyer et al. [9].

Dement Geriatr Cogn Disord Extra 2018;8:60–71
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The total number of cases of both AD and VaD in each Italian region on January 1, 2016 was calculated by applying the prevalence rates of AD and VaD in Europe estimated by Lobo et al. [2] to the total population residing in each Italian region on January 1, 2016 [15].

Adjusted Combined PAR

We estimated separately the PAR for AD and VaD for each of the 7 considered risk factors in both Italy and Europe. To estimate PARs we used Levin's formula [16]: $(P \times (RR - 1)) / (1 + P \times (RR - 1)$, where P is the prevalence of each of the 7 factors in the area of interest, and RR are the relative risks for either AD or VaD for each factor.

Considering the nonindependence of the risk factors, we used the modified version of Levin's formula reported in the study by Norton et al. [3] to estimate the adjusted combined PAR for all 7 risk factors. In the modified formula, $1 - \Pi\ (1 - \omega_i \times \mathrm{PAR}_i)$, ω_i is the unique contribution to each factor estimated as 1 minus the communality of each risk factors and PAR_i is the specific PAR for each risk factors.

Number of Attributable Cases

The number of cases of either AD or VaD attributable to the 7 considered risk factors was calculated by multiplying the adjusted PAR by the prevalence of AD or VaD in either Europe or both overall Italy or single Italian regions.

Impact of Prevention on Prevalence Estimate

We estimated the total number of cases of both AD and VaD in Italy assuming a 20% reduction in the prevalence of each risk factor.

Results

The umbrella review allowed to identify systematic reviews reporting the RRs of VaD for each of the 7 considered modifiable risk factors [17–24]. Table 1 reports the RRs for VaD, the RRs for AD, and the communality estimated by Norton et al. [3].

Results showed that the factors associated with the lowest RRs were diabetes mellitus for AD (1.46) and midlife obesity for VaD (1.33), while the factors associated with the highest RRs were physical inactivity for AD (1.82) and depression for VaD (2.92). The RRs reported for midlife obesity and VaD refer to the risk of being overweight compared to having a normal BMI.

Europe

We used the RRs for VaD and the communality reported in Table 1, and the prevalence estimates of the 7 risk factors in Europe reported by Norton at al. [3], to calculate the PAR for VaD along with its 95% CIs. Table 2 reports the PARs for AD and VaD, the number of cases of AD, VaD or both types of dementia in 2010 attributable to the 7 considered risk factors.

The factors associated with the lowest PARs were diabetes mellitus for AD (3.1%) and midlife obesity for VaD (2.3%), while the factors associated with the highest PARs were physical inactivity for AD (20.3%) and low educational level for VaD (31.8%). Assuming the independence of the considered factors, the combined PAR was 54% for AD and 66.8% for VaD, while assuming the nonindependence of considered factors the adjusted combined PAR was 31.4% for AD and 37.8% for VaD. Under the nonindependence assumption, the total number of attributable cases was 3,033,000 for AD and 873,000 for VaD, with an overall number of 3,906,000 cases of both AD and VaD attributable jointly to the 7 considered risk factors.

Dement Geriatr Cogn Disord Extra 2018;8:60–71
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Table 1. Risk ratios for the 7 lifestyle factors for AD and VaD, and shared variance within each factor

Risk factor	Relative risk (95% CI)		Communality[b], %
	AD	VaD	
Diabetes mellitus	1.46 (1.20–1.77)	2.28 (1.94–2.66)	50.9
Midlife hypertension	1.61 (1.16–2.24)	1.59 (1.20–2.11)	65.0
Midlife obesity	1.60 (1.34–1.92)	1.33 (1.02–1.75)[a]	43.7
Physical inactivity	1.82 (1.19–2.78)	1.61 (1.09–2.38)	49.0
Depression	1.65 (1.42–1.92)	2.92 (1.87–4.56)	37.4
Smoking	1.59 (1.15–2.20)	1.26 (1.05– 1.50)	58.1
Low educational attainment	1.59 (1.35–1.86)	2.75 (2.19–3.45)	45.6

[a] Overweight versus normal BMI groups in midlife. [b] The proportion of the variance in each risk factor shared with the other risk factors.

Table 2. Estimate of the population attributable risk and number of attributable cases in 2010 for AD and VaD

Risk factor	Prevalence[a], %	AD[a]		VaD		Total number (in thousands) of attributable cases in 2010 for AD and VaD
		PAR, % (95% CI)	number (in thousands) of attributable cases in 2010 (95% CI)	PAR[b], % (95%CI)	number (in thousands) of attributable cases in 2010[c] (95% CI)	
Diabetes mellitus	6.9	3.1 (1.4–5.0)	222 (98–364)	8.1 (6.1–10.3)	187 (141–237)	409
Midlife hypertension	12.0	6.8 (1.9–13.0)	492 (136–934)	6.6 (2.3–11.8)	153 (54–271)	645
Midlife obesity	7.2	4.1 (2.4–6.2)	299 (172–448)	2.3 (0.1–5.1)	54 (3–118)	353
Physical inactivity	31.0	20.3% (5.6–35.6)	1,461 (401–2564)	15.9 (2.7–30.0)	367 (63–691)	1,828
Depression	18.5	10.7 (7.2–14.5)	774 (520–1049)	26.2 (13.9–39.7)	605 (320–916)	1,379
Smoking	26.6	13.6 (3.8–24.2)	978 (277–1,745)	6.5 (1.3–11.7)	149 (30–271)	1,127
Low educational attainment	26.6	13.6 (8.5–18.6)	978 (614–1,342)	31.8 (24.0–39.5)	733 (555–910)	1,711
Combined		54.0 (27.2–73.7)	3,891 (1,959–5,311)	66.8 (42.5–83.0)	1,541 (980–1,916)	5,432
Adjusted combined		31.4 (15.3–46.0)	3,033 (1,472–4,332)	37.8 (21.2–52.5)	873 (488–1,211)	3,906

AD, Alzheimer disease; VaD, vascular dementia; PAR, population attributable risk. [a] Estimates from Norton et al. [3]. [b] Estimated using the prevalence from Norton et al. [3] and risk ratio reported in Table 1. [c] Estimated multiplying PAR per number of prevalent cases of VaD in Europe (= 15.8 from Lobo et al. [2]; number of total cases of dementia from Brookmeyer et al. [9]).

Italy

Table 3 reports the prevalence of every considered risk factor both in each single Italian region and in the whole country, the communality of the risk factors in Italy, and the estimated adjusted combined PAR either in basic conditions or assuming a 20% reduction of the frequency of each considered risk factor.

Adjusted combined PARs for Italy were 45.2% for AD and 53.1% for VaD, decreasing respectively to 38.9 and 46.6% when assuming the reduction in the frequency of the risk factors. Communalities ranged from 28.6% for hypertension to 5.1% for smoking (Table 3).

Dement Geriatr Cogn Disord Extra 2018;8:60–71
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Table 3. Prevalence of the 7 risk factors in the Italian regions

Italian regions	Prevalence[a], %							PAR adjustet combined		PAR adjustet combined condidering a reduction of each risk factor by 20%	
	obesity	physical inactivity	smoking	symptoms of depression	hyper-tension	diabetes	low educational attainment	AD	VaD	AD	VaD
Abruzzo	10.9	39.8	29.7	5.2	17.3	3.8	35.2	45.5	52.2	39.1	45.7
Basilicata	9.4	76.07	19.2	3.1	22.7	4.7	40.4	51.7	57.8	45.2	51.4
Calabria	11.2	50.74	24.7	5.8	25.1	6.0	35.6	49.1	56.2	42.6	49.5
Campania	13.6	51.81	28.3	6.6	21.9	6.2	39.5	50.7	57.9	44.1	51.2
Emilia Romagna	11.8	25.78	28.3	7.6	18.6	4.0	36.1	43.1	51.8	36.8	45.3
Friuli Venezia Giulia	10.5	23.37	26	6.4	20.8	3.9	37.1	42.0	51.1	35.8	44.7
Lazio	9.5	36.94	29.1	5.3	19.8	4.4	29.6	44.0	50.3	37.7	43.8
Liguria	8.4	34.03	25.5	6.8	17.0	3.8	32.3	42.5	50.5	36.3	44.0
Lombardia	8.2	25.2	24.3	6.4	18.1	3.5	29.4	39.3	47.5	33.4	41.2
Marche	8.3	29.39	24.1	4.9	20.2	4.2	30.3	40.8	48.4	34.8	42.0
Molise	13.4	29.97	27	10.1	22.9	4.8	22.7	43.3	50.3	37.0	43.6
Piemonte	8	38.74	24.2	5.3	18.7	4.0	38	44.4	52.6	38.1	46.1
Province of Bolzano	7.6	12.84	23.9	4.5	15.6	2.1	48.8	37.8	49.1	32.1	43.2
Province of Trento	7.9	19.73	25.5	4.7	18.5	3.4	32.1	38.0	46.4	32.2	40.2
Puglia	12.4	47.11	25.4	4.0	20.0	5.5	43.6	48.6	56.1	42.1	49.6
Sardegna	10.1	30.69	27	8.4	20.8	5.5	45	46.2	56.4	39.8	49.9
Sicilia	13.3	45.31	28.5	6.3	21.0	6.4	39.4	49.2	56.7	42.6	50.1
Toscana	8.2	33.32	26	6.3	17.3	4.5	36.5	43.3	51.9	37.0	45.5
Umbria	10.2	25.36	30.3	8.2	20.8	4.3	33.3	43.2	51.7	36.9	45.2
Valle d'Aosta	9.6	27.77	25.2	5.7	17.2	3.0	38.9	42.0	50.8	35.9	44.5
Veneto	9.9	26.04	22.7	5.5	20.1	3.8	38.3	41.7	50.9	35.6	44.5
Italy	10.5	36.8	26.4	6.0	19.8	4.7	36.5	45.2	53.1	38.9	46.6
Communality, %	26.4	7.0	5.1	8.4	28.6	26.1	15.8				

Red: worse than national value. Yellow: similar to national value. Green: better than national value.
[a] Source of the PASSI study [10], time interval between 2013 and 2016.

Dement Geriatr Cogn Disord Extra 2018;8:60–71
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Table 4. Number of prevalent cases of AD and VaD on January 1, 2016 in each Italian region either assuming no reduction in the distribution of risk factors, or assuming a 20% reduction in the distribution of risk factors

Italian regions	Resident population on January 1, 2016	AD			VaD		
		prevalent cases on January 1, 2016[a]	considering a reduction of each risk factor by 20%		prevalent cases on January 1, 2016[a]	considering a reduction of each risk factor by 20%	
			prevalent cases	reduction		prevalent cases	reduction
Abruzzo	1,326,513	15,215	14,247	–6.4%	4,574	4,277	–6.5%
Basilicata	573,694	6,231	5,831	–6.4%	1,879	1,758	–6.5%
Calabria	1,970,521	19,132	17,878	–6.6%	5,822	5,433	–6.7%
Campania	5,850,850	45,341	42,327	–6.6%	13,917	12,988	–6.7%
Emilia Romagna	4,448,146	53,310	49,972	–6.3%	15,946	14,912	–6.5%
Friuli Venezia Giulia	1,221,218	15,257	14,315	–6.2%	4,581	4,287	–6.4%
Lazio	5,888,472	57,529	53,919	–6.3%	17,457	16,319	–6.5%
Liguria	1,571,053	22,909	21,497	–6.2%	6,816	6,376	–6.5%
Lombardia	10,008,349	102,578	96,501	–5.9%	31,222	29,246	–6.3%
Marche	1,543,752	19,165	18,007	–6.0%	5,726	5,362	–6.4%
Molise	312,027	3,813	3,573	–6.3%	1,137	1,061	–6.7%
Piemonte	4,404,246	52,641	49,338	–6.3%	15,971	14,942	–6.4%
Province of Bolzano	520,891	4,701	4,433	–5.7%	1,428	1,344	–5.9%
Province of Trento	538,223	5,643	5,316	–5.8%	1,685	1,581	–6.2%
Puglia	4,077,166	38,498	35,987	–6.5%	11,763	11,000	–6.5%
Sardegna	1,658,138	16,602	15,528	–6.5%	5,066	4,736	–6.5%
Sicilia	5,074,261	46,818	43,727	–6.6%	14,273	13,324	–6.7%
Toscana	3,744,398	46,566	43,667	–6.2%	13,965	13,063	–6.5%
Umbria	891,181	11,333	10,622	–6.3%	3,384	3,162	–6.5%
Valle D'Aosta	127,329	1,386	1,301	–6.1%	420	394	–6.3%
Veneto	4,915,123	51,473	48,319	–6.1%	15,581	14,591	–6.4%
Italy	60,665,551	636,141	595,605	–6.4%	192,616	180,026	–6.5%

[a] Estimates based on Lobo et al. [2].

The prevalence of risk factors and the adjusted combined PAR for both AD and VaD varied widely among regions. The frequency of obesity ranged from 7.6% in the Province of Bolzano to 13.6% in the Region of Campania, while the prevalence of physical inactivity ranged from 12.8% in the Province of Bolzano to 76% in the Region of Basilicata, and the frequency of smoking ranged from 19.2% in Basilicata to 30.3% in Umbria. The proportion of people having symptoms of depression ranged from 3.1% in Basilicata to 10.1% in Molise, while the proportion of people having hypertension ranged from 15.6% in the Province of Bolzano to 25.1% in Calabria, and those having diabetes ranged from 2.1% in the Province of Bolzano to 6.4% in Sicilia. The proportion of people having achieved a low educational level ranged from 22.7% in Molise to 48.8% in the Province of Bolzano.

The adjusted combined PAR for AD ranged from 37.8% in the Province of Bolzano to 51.7% in Basilicata, both decreasing to 32.1 and 45.2%, respectively, when applying the 20% reduction in the frequency of all risk factors. The adjusted combined PAR for VaD ranged from 46.6% in the Province of Trento to 57.9% in Campania, both decreasing to 40.2 and 51.2%, respectively, when applying the 20% reduction in all risk factors.

Table 4 reports both the population resident in the whole Italian territory and the population in each single region up to January 1, 2016, the estimated prevalent cases of both AD and VaD up to the same date either considering no reduction of the risk factors or considering

Dement Geriatr Cogn Disord Extra 2018;8:60–71
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a 20% reduction of the prevalence of each considered risk factor. Assuming a 20% reduction of the prevalence of each risk factor, the decrease in the prevalence of AD ranged from 5.8% in the Province of Trento to 6.6% in Calabria, Campania, and Sicilia, while the decrease in the prevalence of VaD ranged from 5.9% in the Province of Bolzano to 6.7% in Calabria, Campania, Molise, and Sicilia.

Discussion

To our knowledge, this is the first study providing evidence on the number of potentially preventable cases of VaD using the same methodology proposed by Norton et al. [3], thus allowing to obtain an estimate of the number of potentially preventable cases of 69.5% (AD + VaD) of all types of dementias. About 3.9 million cases of AD and VaD in Europe could be due to potentially modifiable risk factors. Though Norton et al. [3] suggested that their PAR could be applied to all most common types of dementia, we deem it essential to have a more accurate estimate of the number of potentially preventable cases. This is why we performed a specifically targeted umbrella review to identify the 7 risk factors proven to be associated with VaD and used these factors to estimate our PARs. It is highly probable that each type of dementia is associated with a single specific pattern of risk factors [25–28]. Diabetes mellitus, educational level, and depression have, in fact, a quite different weight as risk factors for either AD or VaD (Table 1).

The adjusted combined PAR depends on the prevalence of the considered risk factors in a specific population, how each factor is defined (including the age range of the sample population, when measured), the proportion of the variance that each risk factor shares with the others (communality), and on the use of specific relative risks, retrieved through available meta-analyses, for each type of dementia.

The PAR allows both researchers and policymakers to estimate the number of cases of each considered condition that could be avoided by implementing interventions aimed at reducing the prevalence of specific risk factors or groups of interacting risk factors [29].

Norton et al. [3], using the relative risks for AD and the other data provided by the Health Survey for England 2006, calculated, for Europe, a 57% combined PAR assuming that risk factors were independent, and a 31.4% adjusted combined PAR assuming that risk factors were not independent. The combined PAR for Australia, calculated using the relative risks and data provided by the Australian Health Survey 2011–2013, was 57% assuming that risk factors were independent, and 48.4% assuming that risk factors were not independent [30]. Almost 30.5% (305,000 cases) of prevalent cases of AD in Germany may be currently attributable to considered risk factors, assuming such factors to be independent [31]. Three more studies have recently been published enrolling populations residing in the Netherlands, Iran, and Canada [32–34], but we could not compare their data with ours due to differences in the methodology used, including the choice of the risk factors to be considered.

The present study estimated, in Italy, a 45.2% adjusted combined PAR for AD (not adjusted combined PAR: 56.8%) and a 53.1% adjusted combined PAR for VaD (not adjusted combined PAR: 65.9%), thus showing that Italy has currently a PAR for AD that is similar to the one estimated for Australia [30].

These findings support the potential of reducing the prevalence of dementia by promoting and implementing tailored interventions targeting these potentially modifiable exposures. Acting on these risk factors could lead to a relevant reduction of the prevalence of dementia, both at a global and at a local level. Moreover, our findings are likely to have underestimated the impact, as we did not include in our analyses mixed dementias (i.e., due to underlying neurodegenerative and vascular conditions), which are highly prevalent among elderly people.

The number of potentially preventable cases of AD, VaD or other types of dementia also depends on the clinical criteria adopted in the prevalence study used as a reference to calculate the number of expected cases. We used the age- and gender-specific prevalence rates of both AD and VaD reported by Lobo et al. [2] to calculate the estimated number of cases of AD and VaD in each Italian region and in the whole country. The clinical criteria that Lobo et al. [2] used in their meta-analysis for the diagnosis of AD and VaD are different criteria than those currently used in clinical practice (i.e., old criteria such as NINCDS-ADRDA, NINCDA-AREN, and DSMIII-R vs. current criteria such as IWG, NIA, and DSM-V). Applying different clinical criteria in a population study can lead to wide differences in prevalence, with up to 10 times higher or lower rates [35]. No population studies are currently available with diagnoses based on the new diagnostic criteria for dementia. These new criteria propose a disease model that starts with a preclinical phase, proceeding in a prodromal phase, and ending in a dementia phase. Based on these new criteria, if we applied the prevalence rates of mild cognitive impairment (included in the DSM-V within the definition of mild neurocognitive disorder), as estimated by the COSMIC (Cohort Studies of Memory in an International Consortium) [36] population study (5.9% for subject older than 60 years), to the Italian population, the number of cases of dementia would further increase from 1 million to almost 2 million [37]. The potential epidemiological impact of this new proposed disease model, and its consistency at a population level, has not been studied yet, but it could still strongly affect all currently available estimates of potentially preventable cases of both AD and VaD. Moreover, we recently published a meta-analysis of 25 studies showing that an overall 18% (95% CIs 14–22) of subjects diagnosed with mild cognitive impairment do, in fact, revert to normal cognition within 2 years of follow-up [38].

We believe that all issues related to the possible prevention of dementia should be included among the priorities of all national dementia plans and in all public health documents on noncommunicable diseases. It would also be useful and beneficial to set up a European monitoring system collecting information for each country.

In order to combine the need for global and consistent estimates with the specificities of individual countries and regions, a harmonization of the methodological approaches to the prevention of dementia should be promoted. In the PAR models, we might assume some "constant" variables that should be consistently and uniformly adopted. Specifically, the use of the same set of diagnostic criteria for dementia, of the same risk estimates for a given risk factor, and of the same models to calculate the communality between risk factors may enhance the consistency and reliability of findings obtained in different settings and circumstances, thus facilitating global reflections. These constant elements may then be combined with variables reflecting the individual characteristics of each specific country and region. In particular, the estimates of prevalent cases, the operational definitions of risk factors, and the sources used for estimating risk and communality should crucially reflect the peculiarities of local contexts in order to more practically drive and inform public health policies.

In conclusion, our study confirms that a relevant reduction in the number of cases of AD and VaD in Europe and Italy may be attributed to potentially modifiable risk factors, thus supporting the need and the potential of possible strategies for the primary prevention of dementia. Recent studies also underlined the role of sensory deprivation and social isolation in the etiology of dementia, thus both should be taken into due consideration in addition to the 7 mentioned risk factors [39]. The variability observed in the estimates obtained for VaD compared to AD, and among the single Italian regions, suggests that public health actions should account for both risk patterns specific to each type of dementia, and for local heterogeneities in the phenomenon.

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